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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
08/444,934	05/22/95	LAWN R	MSM101CONTC

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EXAMINER	
SCHNIZER, H	
ART UNIT	**PAPER NUMBER**
1653	38

DATE MAILED: 05/21/99

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

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Advisory Action

Application No.	Applicant(s)
08/444,934	Lawn et al.
Examiner	**Group Art Unit**
Holly Schnizer	1653

THE PERIOD FOR RESPONSE: [check only a) or b)]

a) ☒ expires 4 months from the mailing date of the final rejection.

b) ☐ expires either three months from the mailing date of the final rejection, or on the mailing date of this Advisory Action, whichever is later. In no event, however, will the statutory period for the response expire later than six months from the date of the final rejection.

Any extension of time must be obtained by filing a petition under 37 CFR 1.136(a), the proposed response and the appropriate fee. The date on which the response, the petition, and the fee have been filed is the date of the response and also the date for the purposes of determining the period of extension and the corresponding amount of the fee. Any extension fee pursuant to 37 CFR 1.17 will be calculated from the date of the originally set shortened statutory period for response or as set forth in b) above.

☐ Appellant's Brief is due two months from the date of the Notice of Appeal filed on _____ (or within any period for response set forth above, whichever is later). See 37 CFR 1.191(d) and 37 CFR 1.192(a).

Applicant's response to the final rejection, filed on *May 3, 1999* **has been considered with the following effect, but is NOT deemed to place the application in condition for allowance:**

☒ The proposed amendment(s):

☒ will be entered upon filing of a Notice of Appeal and an Appeal Brief.

☐ will not be entered because:

☐ they raise new issues that would require further consideration and/or search. (See note below).

☐ they raise the issue of new matter. (See note below).

☐ they are not deemed to place the application in better form for appeal by materially reducing or simplifying the issues for appeal.

☐ they present additional claims without cancelling a corresponding number of finally rejected claims.

NOTE: _____

☐ Applicant's response has overcome the following rejection(s):

_____

☐ Newly proposed or amended claims _____ would be allowable if submitted in a separate, timely filed amendment cancelling the non-allowable claims.

☒ The affidavit, exhibit or request for reconsideration has been considered but does NOT place the application in condition for allowance because:
the request for reconsideration does not avoid any of the rejections set forth in the last office action. (see attachment and office action mailed January 14, 1999.)

☐ The affidavit or exhibit will NOT be considered because it is not directed SOLELY to issues which were newly raised by the Examiner in the final rejection.

☒ For purposes of Appeal, the status of the claims is as follows (see attached written explanation, if any):

Claims allowed: *24 and 25*

Claims objected to: *37*

Claims rejected: *4-6, 8, 20, 21, 23, 27-29, 31-36, and 38-41*

☐ The proposed drawing correction filed on _____ ☐has ☐has not been approved by the Examiner.

☐ Note the attached Information Disclosure Statement(s), PTO-1449, Paper No(s). _____ .

☐ Other

ADVISORY ACTION

Attachment to Paper No. 37

This Advisory Action is in response to Paper #35, filed May 3, 1999. The outstanding rejection is directed to new matter in amended claims directed to a fragment of tissue factor protein consisting of amino acids 1-219, which is the extracellular domain. A summary of the tissue factor protein and variants set forth in the specification that are specific to the claims are discussed below, as well as the Examiner's commentary on the disclosure of the specification and on the Konigsberg Declaration.

At page 3, line 21 ,the specification teaches that "Tissue factor is an integral membrane glycoprotein...". In at least three places in the specification, the membrane spanning region of TF is stated to be the transmembrane domain (TMD) located at about residues 220-242 of the TF protein molecule (see below and Fig. 2.). The transmembrane domain anchors the TF protein in the cell membrane (Page 14, line 25). While the specification does not expressly state that N-terminal to the transmembrane domain is extracellular domain (ECD) and C-terminal to the transmembrane domain is the cytosolic or intracellular domain (ICD), such is art recognized. See the declaration of William H. Konigsberg (Paper #20, filed July 17, 1996) at the middle of page 3 for evidence that the TF protein is comprised of ECD-TMD-ICD. The TF protein consists of 263 amino acids, of which the ECD is 219 amino acid residues in length, the TMD is 24 residues in length, and the ICD is 20 residues in length. Diagrammatically, then, the TF protein can be depicted as three domains as follows:

|----------ECD----------|--TMD--|--ICD--|

The rejection in dispute is whether amended claims directed to the soluble or the ECD fragment of TF protein comprises new matter. It is the Examiner's position that the specification does not teach that the ECD of TF protein should be made or used by itself. Rather, the specification teaches to delete the TMD or hydrophobic portion of the TF protein. The soluble TF protein structure described in the specification is depicted as follows:

|----------ECD----------|--ICD--|

Basis for the soluble protein structure as depicted above is found in the specification. All remarks in the specification regarding deletional variants of TF protein are listed below, bold print being used to highlight precise statements.

At page 1, line 30, the specification states that:

> This invention is also directed to tissue factor protein derivatives, particularly derivatives **lacking the near C-terminal hydrophobic portion of the protein**, and their production by recombinant DNA techniques.

At page 7, line 10, the specification states that:

> This invention is further directed to novel tissue factor protein derivatives, in particular derivatives **lacking** the signal sequence and **the hydrophobic portion**

of the protein near the C-terminal end of the protein comprising the amino acid sequence which constitutes the tissue factor protein transmembrane or membrane binding domain.

At page 9, in the legend for Fig. 5, the specification states that:

The predicted **hydrophobic membrane spanning domain encompasses residues 220-243** and is indicated by the filled bar.

At the paragraph bridging pages 12-13, the specification states:

Deletions are characterized by the removal of one or more amino acid residues from the tissue factor protein sequence. Typically, **no more than about from 2 to 6 residues are deleted at any one site** within the tissue factor protein molecule, although deletion of residues -31 to -1 inclusive will be undertaken to obtain met-tissue factor protein, a variant adapted for intracellular direct expression of met-tissue factor protein. **Another deletion is of the transmembrane domain located at about residues 220 to 242 of the tissue factor protein molecule**.

At page 14, paragraphs 1 and 2, the specification states:

A major class of substitutional or **deletional variants are those involving the transmembrane, i.e. hydrophobic or lipophilic region of the tissue factor protein**. The **transmembrane region of the tissue factor protein is located at about residues 220 to 242** of the protein encoded by the DNA from human adipose tissues. This region is a **highly hydrophobic or lipophilic domain that is the proper size to span the lipid bilayer of the cellular membrane**. It is believed to anchor tissue factor protein in the cell membrane.

Deletion or substitution of the transmembrane domains will facilitate recovery and provide a soluble form of recombinant tissue factor protein by reducing its cellular or membrane lipid affinity and improving its water solubility so that detergents will not be required to maintain tissue factor protein in aqueous solution. **Preferably, the transmembrane domain is deleted**, rather than substituted in order to avoid the introduction of potentially immunogenic epitopes.

> **One advantage of the transmembrane deleted tissue factor protein** is that it is more easily secreted into the culture medium. This variant is water soluble and does not have an appreciable affinity for cell membrane lipids, thus considerably simplifying its recovery from recombinant cell culture.

These five passages omit reference to truncating the TF at the hydrophobic portion and, without inclusion of any statement regarding the deletion of the hydrophilic ICD, these passages specify that only the C-terminal hydrophobic portion (residues 220-243) should be removed from the TF protein. Also, while one skilled in the art would generally understand that a soluble portion of a membrane-bound protein is its ECD, it should be noted that the ECD and the ICD are hydrophilic and therefore deletion of the TMD will result in a soluble protein. The specification is clear that the TMD is to be deleted from the TF protein. The specification does not indicate that the TF protein should be truncated at the TMD or that both the TMD and the ICD should be deleted, resulting in the ECD being by itself.

Furthermore, Applicants contend that they contemplated deletion variants which include both the deletion of the transmembrane region and of other amino acids (see page 6, lines 1-2 of Response under CFR 1.116 filed 5/10/99). However, at page 13, line 10, the specification states:

> However, variant tissue factor protein **fragments having up to about 100-150 residues** may be conveniently prepared by *in vitro* synthesis.

It is clear from the above passage that Applicants contemplated the preparation of tissue factor variants of 100-150 amino acid residues in length. While such fragments may include deletion variants which include deletion of both the TMD and other amino acids, such fragments

do **not** encompass the much larger ECD which is 216 residues. Moreover, the above passage only shows that Applicants considered the possibility of preparing such tissue factor fragments. Therefore, even if the claims were amended such that they were directed to tissue factor protein fragments of up to 100-150 residues, the specification does not disclose any active tissue factor variants of 100-150 residues and thus does not satisfy the written description requirment for tissue factor protein fragments having up to about 100-150 residues.

At page 13, line 30, the specification states:

...and **deletions will range about from 1 to 30 residues**....

Therefore, the specification teaches to delete the TMD of the TF protein and there is no basis in the specification for making the ECD of the TF protein without its fusion to the ICD.

The Konigsberg Declaration has been considered. Konigsberg states at page 3, line 4:

> I believe that those of skill in the arts of proteins, cloning and expression, and tissue factor at that time would have understood the description of deletion of the transmembrane region to tissue factor to include tissue factor protein from which the entire C-terminal region, including the transmembrane and cytoplasmic regions, had been deleted. This is so because the deletion of the transmembrane region as described in the specification would have been viewed and understood as an ***indication*** that the extracellular domain could be used separately from the transmembrane region and the cytoplasmic region.

At the top of page 4, Konigsberg states that:

> ...it is clear, and those of skill in the art at the time would have understood, that **deletion of the transmembrane region is equivalent to deletion of both the transmembrane region and the cytoplasmic region**, since the cytoplasmic domain serves no purpose in the absence of the transmembrane domain. For these reasons, it is my opinion that those of skill in the art at the time the application was filed would have considered the **reference to deletion of the transmembrane region to indicate that the inventors contemplated deletion of the C-terminal portion of the tissue factor, including the cytoplasmic domain**.

These passages in the Declaration do not state that Applicants describe the ECD by itself, but that deletion of the TMD would indicate to those of skill in the art that the ECD could be used by itself. While the Examiner agrees that deletion of the TMD is equivalent *functionally* to the deletion of both the TMD and the ICD, the structures of the resulting proteins are different. Further, Konigsberg's statement that deletion of the TMD indicates that the inventors contemplated deletion of both the TMD and the ICD is speculative in the absence of the disclosure in the specification of the deletion of both domains.

Therefore, the Konigsberg declaration is not persuasive that deletion of the TMD should be taken to mean that both the TMD and the ICD have been removed from the TF protein, leaving the ECD by itself. It is obvious to truncate the TF protein at the TMD; however, the specification is silent regarding such truncation and even specifies that fragments of TF proteins are up to about 150 residues (and thus any N-terminal truncation would be about 70 residues short of the full ECD and C-terminal truncation would include the TMD and ICD), and deletions are of about 1-30 residues (which would not be sufficient for the removal of both the TMD and the ICD together).

That which would have been obvious to the person of ordinary skill in the art is not a substitute for an adequate disclosure under 35 USC 112, first paragraph. As stated in the courts:

> "That a person skilled in the art might realize from reading the disclosure that such a step is possible is not sufficient indication to that person that that step is part of appellents' invention" (*In re Winkhaus* 188 USPQ 129 at 131 (CCPA, 1975)).

"An applicant's specification must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possesion of the invention, i.e., whatever is now claimed" (MPEP 2163, see *Vas-Cath, Inc. v. Mahurkar* 19USPQ2d 1111, 1117 (Fed. Cir. 1991)). In the present case, the specification fails to describe deletion variants other than the deletion variant lacking residues 220 to 243.

In Paper #37, Applicants urge that the Konigsberg Declaration stands for the proposition that once one of ordinary skill in the art understood that the transmembrane region existed and that the cytoplasmic region was unnecessary, one of ordinary skill in the art would interpret a deletion of the transmembrane region to simply refer to a deletion of the entire carboxy portion of the protein from amino acid 220-263. Surely, it is obvious to truncate the TF protein at the TMD; however, that is not what is taught in the specification to do. Applicants argue that removal of the TMD is one way to delete the TMD, but the preferred way is to delete both the

TMD and the ICD. Again, this "preferred way", or best mode, is not disclosed in the specification.

Applicants cite page 14 of the specification to urge that deletions "involving" the TMD include deletion of other amino acid residues. The passage is cited above and again here below:

> A major class of substitutional or **deletional variants are those involving the transmembrane, i.e. hydrophobic or lipophilic region of the tissue factor protein**. The **transmembrane region of the tissue factor protein is located at about residues 220 to 242** of the protein encoded by the DNA from human adipose tissues. This region is a **highly hydrophobic or lipophilic domain that is the proper size to span the lipid bilayer of the cellular membrane**. It is believed to anchor tissue factor protein in the cell membrane.

In no place does the specification teach to delete the ICD. Indeed, this passage is directed solely to the deletion of the TMD.

At page 6, Applicants state that the Declaration is expert opinion and that the Examiner's arguments are not supported by evidence made of record. The Examiner agrees with the Declaration of Konigsberg. Surely, deletion of the TMD is equivalent to deletion of the TMD and the ICD together. However, the latter is not disclosed in the specification. Deletion of the TMD renders it obvious to delete the ICD as well. However, again, the latter is not disclosed in the specification.

Applicants remaining arguments center around whether the ECD is described in the specification. The ECD is set forth to be amino acids 1-219 of the full-length TF protein. The

specification does not teach to make the ECD amino acids 1-219 of full-length by itself, but fused to the ICD via the deletion of the TMD.

In Paper #38, faxed May 12, 1999, Applicants present arguments found convincing in the corresponding European patent application, Opposition by Diagnostica Stago. The Examiner has read this Opposition. The discussion is too limited for the Examiner to determine why the European examiner accepted the deletion of the TMDin TF protein to include the ICD.

Applicants draw attention to page 7 of the specification and point out that terms such as "comprising" are open language. Without specifically pointing out what else deletion of the TMD includes, it cannot be stated that the entire ICD will also be removed, or if any or all of the ECD will be removed.

Other arguments have been previously addressed.

Karen Cochrane Carlson PhD

HS
Holly Schnizer
May 17, 1999

KAREN COCHRANE CARLSON, PH.D
PRIMARY EXAMINER